Hematocrit Level as a Marker of Outcome in ST-Segment Elevation Myocardial Infarction

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Anemia is a well-known predictor of a poor outcome in patients with ST-segment elevation myocardial infarction (STEMI). In contrast, data relating erythrocytosis to clinical outcomes in patients with STEMI are limited. Because erythrocytosis predisposes to a prothrombotic state, we hypothesized it would be associated with an increased risk of thrombotic complications in patients with STEMI undergoing primary percutaneous coronary intervention. We studied 1,042 consecutive patients with STEMI who underwent primary percutaneous coronary intervention and were a part of our primary percutaneous coronary intervention registry from 2001 to 2007. Patients with cardiogenic shock and late arrival were excluded. Patients were allocated into 3 groups according to their baseline hematocrit: anemia (<36% for women and <39% for men), normal, erythrocytosis (>46% for women and >47% for men). The clinical outcomes were assessed at 1, 6, and 12 months. The patients with anemia had the greatest clinical risk profile. Patients with erythrocytosis had a lower risk profile than the other 2 groups, except for greater rates of smoking. The mortality rates were greatest among the patients with anemia, followed by the patients with erythrocytosis, who in turn had greater short-term mortality than patients with normal hematocrit. Multivariate analysis, which included patients with erythrocytosis and those with normal hematocrit (excluding the patients with anemia), revealed that erythrocytosis was associated with an odds ratio of 4.3 (95% confidence interval 1.4 to 13, p = 0.01) for 1-month mortality. In conclusion, although not as strong a predictor of mortality as anemia, erythrocytosis might be associated with increased short-term mortality compared to a normal hematocrit. The measurement of hematocrit can be used as a useful prognostic marker in patients with STEMI. **(Am J Cardiol 2010;105:435–440)**

In contrast to anemia, which has been clearly related to poor outcomes in various cardiac conditions, the data regarding erythrocytosis and the clinical outcomes of patients with ST-segment elevation myocardial infarction (STEMI) are limited. Sabatine et al[1] reported that in patients with acute coronary syndromes (ACS) both high and low hemoglobin levels were associated with increased rates of mortality (for STEMI, hemoglobin levels >17 g/dl or <14 g/dl; and for non-STEMI, hemoglobin levels >16 g/dl or <11 g/dl). However, the present study consisted of patients with ACS from 16 Thrombolysis in Myocardial Infarction (TIMI) trials. The STEMI cohort included patients treated mainly with various thrombolytic drugs rather than primary percutaneous coronary intervention (PCI).[1] Thus, data regarding patients with STEMI and relatively high hemoglobin levels, who were treated with contemporary primary PCI are lacking. Erythrocytosis and polycythemia have been associated with adverse outcomes in various populations. High hematocrit values have been related to an increased risk of development of atherosclerosis and cardiovascular disease.[2–4] In addition, high hemoglobin levels were shown to increase blood viscosity, which, in turn, can cause increased coronary vascular resistance, decreased coronary blood flow, and a predisposition to thrombosis.[5–7] We, therefore, hypothesized that patients with STEMI and erythrocytosis on admission, who were treated with primary PCI, would be prone to a greater risk of thrombotic complications. Accordingly, we investigated the clinical outcome of patients with STEMI and erythrocytosis on admission who underwent primary PCI.

Methods

From January 2001 to December 2007, 1,165 consecutive patients with chest pain and STEMI who underwent emergency PCI at the Rabin Medical Center, Tel Aviv, Israel, were prospectively observed and their data entered into a clinical database. Acute STEMI was defined as the presence of typical chest pain and accompanying symptoms for ≥30 minutes but <12 hours in the presence of ST-segment elevation of ≥1 mm in ≥2 contiguous leads or new or undetermined duration of left branch bundle block in association with a ≥2 times increase in cardiac enzymes (troponin I or T). The data included demographic, clinical, angiographic, and procedural data. The ethics committee of

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Table 1
Clinical characteristics

Variable	Hematocrit <39% or <36% (n = 208)	Normal (n = 718)	Hematocrit >47% (n = 116)	p Value	
				3 Group Comparison	Normal vs Hematocrit >47%
Age (years)	66 ± 13	60 ± 12	55 ± 12	0.0001	0.001
Women	53 (26%)	133 (19%)	4 (3.5%)	0.0001	<0.0001
Diabetes mellitus	69 (33%)	179 (25%)	19 (16%)	0.001	0.04
Renal insufficiency*	58 (28%)	72 (10%)	11 (9.5%)	0.001	0.9
Hypertension	124 (60%)	302 (42%)	39 (34%)	0.0001	0.08
Current smoker	58 (28%)	337 (47%)	72 (62%)	0.0001	0.002
Previous myocardial infarction	24 (12%)	86 (12%)	12 (10.5%)	0.9	0.6
Previous coronary intervention	33 (16%)	93 (13%)	9 (8%)	0.1	0.1
Previous coronary bypass grafting	8 (3.9%)	14 (2.0%)	4 (3.5%)	0.2	0.3
Previous peripheral vascular disease	16 (7.8%)	27 (3.8%)	7 (6.1%)	0.05	0.25
Previous stroke	20 (9.8%)	29 (4.0%)	0	0.0001	0.03
Ejection fraction <40%	85 (41%)	302 (42%)	55 (47%)	0.6	0.3
Anterior wall myocardial infarction	94 (45%)	337 (47%)	62 (53%)	0.6	0.2
Hemoglobin (g/dl)	11.5 ± 1.0	14.1 ± 0.9	16.3 ± 0.7	0.0001	0.001
White blood cell count (1,000/μl)	11.2 ± 4.0	12.2 ± 4.1	14.5 ± 10.0	0.0001	0.005
Platelet count (1,000/μl)	270 ± 104	258 ± 67	260 ± 71	0.2	0.6
Peak creatine kinase ($\times 10^3$ U/L)	1.8 ± 1.8	2.0 ± 1.9	2.5 ± 2.4	0.009	0.03
Killip class >1	42 (20%)	93 (13%)	20 (17%)	0.03	0.2
CADILLAC score	6.9 ± 3.8	3.6 ± 3.2	3.6 ± 3.3	0.001	0.9

* Creatinine clearance <60 ml/min/m^2.
CADILLAC = Controlled abciximab and Device Investigation to Lower Late Angioplasty Complication.

Table 2
Previous medications and intervals

Variable	Hematocrit <39% or <36% (n = 208)	Normal (n = 718)	Hematocrit >47% (n = 116)	p Value
Medications				
Aspirin	185 (89%)	668 (93%)	110 (95%)	0.1
Clopidogrel pretreatment	87 (42%)	337 (47%)	52 (45%)	0.6
β Blockers	23 (11%)	101 (14%)	14 (12%)	0.6
Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers	21 (10%)	79 (11%)	6 (5.6%)	0.2
Statins	83 (40%)	237 (33%)	39 (29%)	0.2
Intervals				
Symptom onset to emergency department (hours)	2.2 ± 2.5	2 ± 2.4	2 ± 2.5	0.5
Emergency department to coronary intervention (hours)	1.4 ± 1.5	1.2 ± 1.5	1.4 ± 1.4	0.6

the Rabin Medical Center approved this registry. The patients were excluded from the present analysis if they presented with cardiogenic shock or arrived >12 hours after the beginning of chest pain. A total of 1,042 patients were included in the present study. They were allocated into 3 groups according to their baseline hematocrit level at admission: (1) anemia, hematocrit <36% for women and <39% for men[8] (n = 208); (2) normal, hematocrit 36% to 46% for women and 39% to 47% for men (n = 718); and (3) erythrocytosis, hematocrit >46% for women and >47% for men (n = 116).

All patients were treated with aspirin 325 mg before PCI and clopidogrel 300 to 600 mg either before PCI or immediately after PCI. Unfractionated heparin (70 U/kg loading) was given before PCI and adjusted to achieve an activated clotting time of 200 to 250 seconds during the procedure. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Coronary angiography was performed through the femoral route. The selection of stent type, predilation with undersized balloons, and postdilation with larger balloons were also left to the operator's discretion. All stents were implanted using a moderate to high deployment pressure (12 to 16 atm). All patients were prescribed lifelong aspirin and clopidogrel (75 mg/day) for 3 to 12 months, depending on the stent type. The baseline clinical characteristics, angiographic details, and clinical outcomes were collected.

Coronary angiograms were recorded at baseline and after PCI. They were analyzed by experienced cardiologists at our angiography core laboratory using the MDView QA System (Medcon Telemedicine Technology, Tel-Aviv, Israel). The cardiologists were unaware of the group allocation of the patients. Analysis was performed using automated edge-detection techniques. The contrast-filled guiding catheter (6F or 7F) was used for calibration. Standard morphologic criteria were used to identify the lesion location, lumen diameter, presence of thrombus, Thrombol-

Table 3
Angiographic and procedural characteristics

Variable	Hematocrit <39% or <36% (n = 208)	Normal (n = 718)	Hematocrit >47% (n = 116)	p Value	
				3 Group Comparison	Normal vs Hematocrit >47%
Culprit artery					
Left anterior descending	90 (43%)	323 (45%)	62 (53%)	0.2	0.1
Left circumflex	23 (11%)	100 (14%)	21 (18%)	0.2	0.25
Right coronary	87 (42%)	259 (36%)	30 (26%)	0.2	0.1
Multivessel disease	135 (65%)	388 (54%)	74 (64%)	0.25	0.05
Preintervention Thrombolysis in Myocardial Infarction flow 0-1	139 (67%)	452 (63%)	73 (63%)	0.7	1
Postintervention Thrombolysis in Myocardial Infarction flow 3	195 (94%)	689 (96%)	108 (93%)	0.6	0.2
Preintervention culprit stenosis	96 ± 9%	96 ± 7%	96 ± 7%	0.8	1
Postintervention culprit stenosis	4 ± 4%	4 ± 3%	5 ± 4%	0.5	0.4
Preintervention reference diameter (mm)	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.6	0.8	0.9
Postprocedure minimal lumen diameter (mm)	3 ± 0.7	3.1 ± 0.6	3.1 ± 0.8	0.3	0.9
No reflow	14 (6.5%)	42 (5.8%)	6 (5.4%)	0.9	0.8
Glycoprotein IIb/IIIa inhibitors	131 (63%)	574 (80%)	96 (83%)	0.0001	0.5
Visible thrombus	177 (85%)	610 (85%)	100 (86%)	0.9	0.7
Thrombectomy devices	19 (9.3%)	40 (5.6%)	4 (3.5%)	0.2	0.3
Drug-eluting stents	27 (13%)	122 (17%)	21 (18%)	0.5	0.8
Mean stent width (mm)	3.1 ± 0.4	3.1 ± 0.5	3.2 ± 0.4	0.2	0.5
Procedural success	195 (94%)	689 (96%)	111 (93%)	0.5	0.9

ysis in Myocardial Infarction flow grade, and no reflow. On the basis of these measurements, the percentage of diameter stenosis was determined before and after PCI.

The immediate and in-hospital events were recorded from the hospital charts. For each patient, a standardized questionnaire was completed either by telephone or in the outpatient clinic at the 1-, 6-, and 12-month follow-up visits. Mortality was confirmed from the records of the Interior Ministry of Israel. Repeated revascularization procedures and episodes of reinfarction were confirmed using the hospital and affiliated hospital databases. These databases were searched for all patients in the study to gather information regarding repeated events. The follow-up data were complete for 100% of the patients at 1 month. At 12 months, mortality data were available for 100% of the patients, and revascularization and reinfarction data were available for 94% of the patients. Procedural success was defined as angiographic residual stenosis of <20% by visual estimate or quantitative coronary angiography. The diagnosis of reinfarction was determined from recurrent chest pain suggestive of acute myocardial infarction accompanied by repeated increases in cardiac enzymes to ≥2 times the upper limit of normal ≥48 hours after PCI and/or new ST elevation or pathologic Q waves. Target vessel revascularization was defined as any revascularization that involved the target vessel. Stent thrombosis was defined according to the Academic Research Consortium definitions as definite in the context of ACS and/or reinfarction in the culprit coronary territory with angiographically proven thrombosis (thrombus or occlusion) of the previously implanted stent.[9] Major adverse cardiac events at 12 months included cardiac death, nonfatal myocardial infarction, or target vessel revascularization (without repetition). All events were further adjudicated by an experienced cardiologist from our research team.

Continuous variables are presented as the mean ± SD, and categorical variables, as frequencies (percentages). Comparisons were performed among the 3 study groups and separately between the erythrocytosis and normal groups. Continuous variables were compared using unpaired Student's *t* tests. Categorical variables were compared using chi-square statistics or Fischer's exact test, as appropriate. Multivariate logistic regression analysis was performed to determine the significance of variables related to 1-month mortality among all 3 groups and, separately, among patients with erythrocytosis and a normal hematocrit (excluding patients with anemia). The model included all clinical variables with $p < 0.1$ on univariate analysis. Analyses were performed using Statisca software (StatSoft, Tulsa, Oklahoma), and $p < 0.05$ was considered significant.

Results

A total of 1,042 patients with STEMI, who were treated with primary PCI, were included in the present study. According to their baseline (admission) hematocrit values, 208 (20%) had anemia, 116 (11%) had erythrocytosis, and 718 (69%) had normal hematocrit values. The baseline clinical characteristics are presented in Table 1. Patients with anemia had the greatest risk profile—they were older; were more likely to be women; were more likely to have diabetes, renal insufficiency, hypertension, peripheral vascular disease, and previous stroke; and were more likely to present with Killip class >1 and a high Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) score. Overall, the patients with erythrocytosis had a lower risk profile than those in the other 2 groups. When compared with the "normal" group, patients with erythrocytosis were younger and less likely to be women or to have diabetes, hypertension (trend), or previ-

Table 4
Clinical outcomes

Variable	Hematocrit <39% or <36% (n = 208)	Normal (n = 718)	Hematocrit >47% (n = 116)	p Value	
				3 Group Comparison	Normal vs Erythrocytosis
At 1 month					
Mortality	15 (7.3%)	16 (2.2%)	6 (4.8%)	0.002	0.07
Reinfarction	16 (7.7%)	15 (2.1%)	4 (3.2%)	0.0004	0.4
Stent thrombosis	8 (3.9%)	12 (1.7%)	2 (1.7%)	0.15	1
At 6 months					
Mortality	19 (9%)	29 (4%)	8 (7.2%)	0.01	0.15
Reinfarction	23 (11%)	28 (3.9%)	6 (5%)	0.0004	0.6
Stent thrombosis	12 (6%)	19 (2.7%)	3 (2.7%)	0.07	1
At 12 months					
Mortality	21 (10.3%)	42 (5.9%)	10 (8.7%)	0.07	0.2
Reinfarction	27 (13%)	43 (6%)	6 (4.8%)	0.002	0.7
Stent thrombosis	15 (7%)	22 (3%)	3 (2.9%)	0.02	0.8
Target vessel revascularization	33 (16%)	60 (8.3%)	8 (7.1%)	0.003	0.6
12-mo MACE	65 (31%)	154 (21%)	27 (23%)	0.01	0.7

MACE = major adverse cardiac events (death, nonfatal reinfarction, and target vessel revascularization).

Table 5
Multivariate analysis of variables related to 1-month mortality among patients with erythrocytosis and normal hematocrit

Variable	Odds Ratio	95% Confidence Interval	p Value
Age >65 years	1.2	0.8–2.1	0.15
Female gender	1.4	0.6–4.6	0.2
Diabetes	2.4	0.8–6.7	0.1
Renal insufficiency*	1.65	1.1–2.4	0.008
Hypertension	0.8	0.3–2.1	0.6
Smoking	1	0.98–1	0.3
Previous stroke	4.4	1–19.5	0.05
Erythrocytosis	4.3	1.4–13	0.01
White blood cell count >15,000/μl	3.9	1.5–10	0.005
Peak creatine kinase >1,000 U/L	2.5	0.98–6.5	0.055
Multivessel disease	1.2	0.5–3.9	0.4

* Creatinine clearance <60 ml/min/m^2.

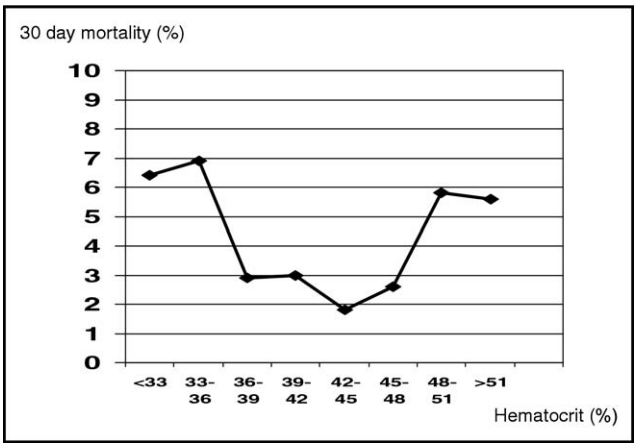

Figure 1. One-month mortality as function of baseline hematocrit level in patients with STEMI treated with primary PCI. Mortality rates were greatest among patients with anemia, followed by patients with erythrocytosis. Lowest event rates occurred in patients with normal hematocrit levels.

ous stroke. The only exception was a greater rate of current smokers among patients with erythrocytosis compared to the other 2 groups. Previous medical treatment and the intervals from the onset of chest pain to arrival at the emergency department and performance of PCI were similar among the 3 groups (Table 2). The angiographic and procedural characteristics were also similar among the 3 groups (Table 3), apart for a lower rate of glycoprotein IIb/IIIa inhibitor use among patients with anemia and a greater likelihood of multivessel disease among patients with erythrocytosis than in patients with a normal hematocrit.

The clinical outcomes are presented in Table 4. In accordance with their high-risk profile, patients with anemia had greater rates of mortality and reinfarction at 1, 6, and 12 months and greater rates of stent thrombosis, target vessel revascularization, and major adverse cardiac events at 12 months than did the other 2 groups. On multivariate logistic regression analysis, anemia was associated with an odds ratio of 3.5 (95% confidence interval 1.6 to 7.5, p = 0.001) for 1-month mortality. Comparing patients with erythrocytosis and patients with normal hematocrit, those with erythrocytosis tended to have a greater rate of 1-month mortality (4.8% vs 2.2%, respectively; p = 0.07). Although mortality was also greater at 6 and 12 months for patients with erythrocytosis compared to those with a normal hematocrit, these differences were not statistically significant (p = 0.15 to 0.2). Multivariate logistic regression analysis, performed to determine the variables related to 1-month mortality among patients with erythrocytosis and those with a normal hematocrit (excluding patients with anemia), included the main characteristics that differed between the 2 groups (age, gender, diabetes, smoking, hypertension, multivessel disease). Erythrocytosis was associated with an odds ratio of 4.3 (95% confidence interval 1.4 to 13, p = 0.01) for 1-month mortality. Other factors in the model that were

associated with 1-month mortality were renal insufficiency, previous stroke, peak creatinine level, and white blood cell count (Table 5).

When plotting the 1-month mortality and baseline hematocrit levels, an inverse J-shaped curve was obtained, with the greatest mortality rates among patients with anemia, followed by patients with erythrocytosis, and the lowest event rates observed at a hematocrit of 36% to 48%, reflecting the normal hematocrit range (Figure 1).

Discussion

Abundant research has been devoted to search for prognostic factors that have predictive value for the outcomes of patients with ACS. Several risk scores (eg, CADILLAC, Thrombolysis in Myocardial Infarction, and Global Registry of Acute Cardiac Events [GRACE] risk scores), and serum biomarkers (eg, troponin, C-reactive protein, and brain natriuretic peptide) have been used for this purpose. The search for new biomarkers that are readily available and cost-effective is of special interest. Important prognostic information can be learned from routine hematologic tests. Anemia is a strong and well-established predictor of adverse cardiovascular outcomes in both ACS and heart failure.[1,10–12] In accordance with previous data, our results have clearly demonstrated the increased risk associated with anemia on admission for short- and long-term mortality, reinfarction, and total major adverse cardiac events in patients with STEMI.

The role of erythrocytosis in predicting cardiovascular events in patients with ACS is less well established. To our knowledge, this is the first study to examine the prognostic value of erythrocytosis on admission in patients with STEMI treated with primary PCI. We found that compared to patients with normal hematocrit levels, patients with erythrocytosis tended to have greater short-term (1-month) mortality, despite a relatively lower risk profile. Multivariate analysis, which considered the main clinical characteristics that differed between the 2 groups, strengthened these findings. Our study, therefore, has extended the findings of Sabatine et al[1] to patients with STEMI treated with a contemporary approach of primary PCI. The increased risk associated with erythrocytosis in our study subsided with time and was no longer statistically significant at 6 and 12 months. Two reasons are possible for this change over time and the lack of a long-term effect. First, nearly all patients were treated at discharge with aspirin, clopidogrel, and statins. These 3 drugs might have attenuated the predisposition to thrombosis that has been described in relation to erythrocytosis. Second, erythrocytosis might be, at times, a temporary reactive occurrence secondary to relative dehydration for instance.

Erythrocytosis and polycythemia have been associated with adverse cardiovascular events in various populations. Wu et al[13] reported that in patients undergoing noncardiac surgery, even mild degrees of preoperative polycythemia (defined by increased hematocrit levels) were associated with an increased risk of 30-day postoperative mortality and cardiac events. The Framingham study data have shown that elevated hematocrit levels are related to the incidence of cardiovascular disease, including coronary artery disease and myocardial infarction, as well as mortality.[3] Similar to our results, in the Framingham study a J- or U-shaped relation between the hematocrit level and cardiovascular events was noted.[3] Recently, Aoki et al[14] reported that increased baseline hemoglobin levels was one of the strong predictors of the development of early stent thrombosis after PCI in patients with ACS.[14] These data, along with our findings of increased short-term mortality in patients with STEMI presenting with erythrocytosis, support the hypothesis that erthrocythosis might predispose to thrombotic–ischemic complications, possibly because of increase blood viscosity and increased coronary vascular resistance.[5–7]

The present study had several limitations. First, the study was based on a registry with all the limitations inherent to a nonrandomized study. Second, profound differences and imbalances were present among the 3 study groups, mainly in the clinical characteristics. However, we attempted to overcome this limitation by using multivariate logistic regression analysis to minimize potential confounders. Third, unlike anemia, the criteria for defining erythrocytosis are not uniform and the distinction between erythrocytosis and polycythemia (vera) is, at times, difficult to establish. We did not have data on erythropoietin levels. Regarding other blood cells, no differences were found among the 3 groups in platelet counts; however, the white blood cell counts were greater in the patient group with erythrocytosis compared to those with anemia or normal hematocrit (Table 1). When using cutoff values for erythrocytosis other than the one we used, very similar results for clinical outcomes were obtained (data not shown). Despite these limitations, our results have highlighted the prognostic importance of the hematocrit value at admission in patients with STEMI undergoing primary PCI.

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